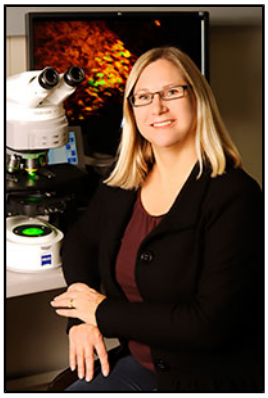
NIH scientists study brain region required for social aggression

By Robin Arnette

A black bear may mark its territory by rubbing its back on trees or leaving bite and claw marks in the wood. If another bear enters the area, the first bear will determine whether the intruder is a friend or foe and act accordingly. New research from the National Institutes of Health has identified a region of the brain that may be responsible for interpreting these social cues and responding with aggressive behavior.

Researchers from NIEHS and the National Institute of Mental Health (NIMH) were the first to demonstrate that a specific area of the hippocampus, a part of the brain involved in learning and memory, allows animals to assess and respond to social threats. The study, which appeared online May 27 in the journal Molecular Psychiatry, may help scientists better understand the network of neurons involved in social recognition memory and aggression.



Several years ago, Dudek's group found that caffeine strengthens connections on CA2 neurons, which may make people and animals learn faster (see story (http://irp.nih.gov/catalyst/v20i1/coffee-may-boost-learning-potential)). This recent study found that although vasopressin uses a slightly different mechanism, it acts on the same neurons that get a buzz with caffeine. (Photo courtesy of Steve McCaw)

Neurohormone acts on particular group of neurons

Serena Dudek, Ph.D., leads the NIEHS Synaptic and Developmental Plasticity Group and studies neurons in the CA2 region of the hippocampus. NIMH colleague Scott Young, M.D., Ph.D., also examines CA2, so he suggested they collaborate on a project. Young focuses on a neurohormone receptor that appears in the brain exclusively in the CA2.

Young (http://www.nimh.nih.gov/labs-at-nimh/principal-investigators/w-scott-young.shtml) and his group are interested in the effects of vasopressin, a neurohormone linked to social behavior. When they developed knockout mice that lacked the vasopressin 1b receptor (Avpr1b), they observed that these mutant mice had extremely poor recall of mice they had seen before, but importantly, they were also less aggressive. These mice could still recognize and attack prey, but their docile state prevented the Avpr1b knockout males from fighting off other mice that entered their area.

In this study, Young's group added Avpr1b back to the CA2 region of the knockouts, and restored their aggressiveness in response to a social threat.

"This experiment points to the CA2 and the vasopressin 1b receptor as enabling the evaluation of social cues and subsequent aggressive response if appropriate," Young said.

Dudek wondered what effects vasopressin had on neurons in normal rats and mice, so her group measured the synaptic responses, or the electrical result of stimulating the CA2 region. They found that either vasopressin or a selective vasopressin 1b receptor agonist caused a considerable increase in CA2 synaptic response, an effect that did not occur in neurons from Avpr1b knockout mice.

Young is head of the Section on Neural Gene Expression at NIMH, which investigates the roles and regulation of vasopressin and oxytocin expression in the central nervous system. (Photo courtesy of Scott Young)

A mother's job - guarding her children

If the black bear in the example is a female with cubs, another neurohormone would flood her brain. Oxytocin, like vasopressin, is linked to social behavior, but is commonly associated with maternal nurturing of offspring.

Because oxytocin and vasopressin have similar chemical structures, Dudek compared their effects on CA2 and learned that they both caused increases in synaptic responses.

Dudek also tested their effects on neurons from a line of knockout mice Young's team created that lacked the oxytocin receptor (Oxtr). She found that vasopressin still increased synaptic responses in CA2, while the effects of oxytocin were lost.

"Even though they were different hormones, vasopressin and oxytocin enhanced synaptic transmission the same way," Dudek said. "In the end, they had the same effects on CA2 synapses."

Dudek speculated that female Oxtr knockout mice would not respond aggressively to safeguard their pups from harm.

CA2-related illnesses in humans

Work from other groups has found that some CA2 neurons are lost with schizophrenia, and that minor changes in Avpr1b sequence are associated with childhood aggression and some autistic traits. Although the hippocampus is more commonly associated with memory functions, Dudek said older studies indicated that it may also be important in modulating aggression. She hopes this work will lead to the development of pharmaceutical agents that may be used to treat some symptoms of psychiatric disorders.

"The neural pathways that vasopressin and oxytocin employ are complicated, but we know they can act with mechanisms that are similar to ones the brain uses for memory," Dudek said.

Citation: Pagani JH, Zhao M, Cui Z, Williams Avram SK, Caruana DA, Dudek SM, Young WS. (http://www.ncbi.nlm.nih.gov/pubmed/24863146) 2014. Role of the vasopressin 1b receptor in rodent aggressive behavior and synaptic plasticity in hippocampal area CA2. Mol Psychiatry; doi:10.1038/mp.2014.47 [Online 27 May 2014].

Meilan Zhao, Ph.D., is a biologist in Dudek's group and shared first authorship on the paper with two colleagues at NIMH. (Photo courtesy of Steve McCaw)

A mother deer can be aggressive if she thinks her young are in danger. Dudek determined that oxytocin and vasopressin have a similar mode of action on CA2 neurons. Oxytocin may allow a mother deer to recognize and respond to threats. (Photo courtesy of Steve McCaw)

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